II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claim 6 has been amended simply to add a period at the end. Claim 7 has been canceled. Claims 6, 8-9 and 14-23 are pending.

B. Information Disclosure Statements

An information disclosure statement, PTO form 1449 and copies of documents are enclosed.

C. Section 112, First Paragraph Rejections

The Action first rejects claim 6 and 16-20 under 35 USC 112, first paragraph, with the Action taking the position that while the specification is enabling for a method for measuring the amount of oxidative stress by detecting the amount of DNA damage, it does not reasonably provide enablement for detecting mtDNA damage by measuring mt mRNA production, mt protein production, mt oxidative phosphorylation, mt ATP production or changes in oxidative redox state.

In response, Applicants submit that the Action fails to set forth any cognizable evidence to support its position of non-enablement and, as such, has failed to set forth a *prima facie* case based on substantial evidence as the law requires. *In re Gartside*, 203 F.3d 1305, 1315 (Fed. Cir. 2000). To make out a *prima facie* rejection, an examiner is required to come forward with evidence or sufficient reasoning substantiating the doubts advanced. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (C.C.P.A. 1974). The Examiner has attempted to address this issue merely by what

appears to be facts within the examiner's own personal knowledge, which facts have not been substantiated on this record as required by 37 C.F.R. 1.104(d)(2). Thus, if the Examiner persists in this rejection, and continues to rely on the personal knowledge discussed below, she is required to submit an affidavit setting forth this knowledge with particularity.

Before turning to the specifics of the rejection, Applicants first point out that the real "enablement" question here is whether one of skill in the art can carry out the assay as claimed – *i.e.*, whether one of skill in the could undertake a measurement of mt mRNA production, for example. Yet, there has been no suggestion in the Action that one of skill in the art would not be enabled to carry out such an assay, merely whether such an assay would be reasonably predictive of mtDNA damage. Thus, the question is perhaps more appropriately considered one of operability/utility.

The Action Fails to Set Forth Evidence of Unpredictablity

Turning to the Action's comments, in an attempt to satisfy the *Wands* criteria, the Action first takes the position that that the relationship between mitochondrial ("mt") DNA damage is not quantitatively related to mt mRNA production, mt protein production, mt oxidative phosphorylation, mt ATP production or changes in oxidative redox state, and yet provides no support for this conclusion. Rather, the Action simply states that the "art teaches that tissue ischemia, OXPHOS gene defects, environmental toxins, mtDNA mutations, decreased cellular ATP and oxygen radical formation all affect phosphorylation dysfunction which leads to tissue degeneration and cell death" referring to the article of Corral-Debrinski *et al.*, 1992. Action at page 4.

In response to this statement, while the Action did not include a copy of the Corral-Debrinski *et al.* article, the statement attributed to that article does not appear particularly unreasonable on its face; yet it in no way supports a conclusion that the claimed invention lacks enablement or that the art is unpredictable. Thus, it cannot be seen how this statement, even if true, supports the Examiner's position. The fact that the prior art has or has not recognized a correlation relied upon by the present invention simply means that the claims are inventive, and has no bearing, we submit, on the enablement or operability of the invention.

That same paragraph concludes that the "art does not teach how the amount of mtDNA damage is affected or associated by each of these factors." We disagree. The article of Ballinger *et al.* (*Circulation Research* 2000, 86:960-66; copy enclosed) shows that mtDNA damage leads to MT protein damage and mitochondrial dysfunction. Moreover, there are numerous papers that show correlations in an observational way. For example, in Cadenas *et al.* (*Free Radical Biology and Medicine* 29: 222-230 (2000); copy enclosed), in the section entitled "Oxidative inactivation and proteolytic degradation of mitochondrial proteins" that starts on page 227, this is discussed in detail, comparing the effects of different ROS. Similarly, Halmosi *et al.* (*Molecular Pharmacology* 59: 1497-1505 (2001); copy enclosed) shows that PARP inhibitors protect against oxidative DNA breaks (total, not just mitochondrial) and then on mitochondrial function. One of the proteins they measure is cytochrome C, which was also measured by the present inventors. Further, Williams *et al.* (*J. Biol. Chem.* 273: 28510-28515; copy enclosed) looked at mitochondrial function in one of the same models the present inventors have used (SOD2 +/- mice, the mitochondrial SOD) and also report decreased mitochondrial function having to do with rates of oxidative phosphorylation. Thus, contrary to the Examiner's position, the art does demonstrate a correlation.

Guidance in the Specification – Working Examples

The Action next points out the support in the specification for the subject matter of the rejected claims, and concludes that there is insufficient exemplary support to demonstrate that the claimed invention is operable with respect to the various alternative "indirect" methods for measuring mt DNA damage. We submit that the presence or absence of working examples is ordinarily an insufficient basis for finding non-enablement. *Ex parte Nardi*, 229 USPQ 79 (BPAI 1986). This is particularly true where, as here, the question is not whether one of skill can appropriately carry out the assay, it is really whether the assay is reasonably predictive of mtDNA damage.

In an attempt to support a conclusion of non-operability, the Action states at the top of page 5, that an mtDNA mutation could lead to a protein production of zero and that this would, according to the Examiner, not provide any guidance as to the quantity of DNA damage.

We would respond to this by observing that the examiner's scientific reasoning, which is unsupported by any affidavit or art, is totally unfounded and contrary to what a scientist would expect, which is that the ultimate expression of a particular mt gene would very definitely be directly related to the amount of random damage in that particular gene. For example, let's say we have a population of 100 mitochondria, each having one gene coding for "X". If 20 of the 100 mitochondria have mutational "hits" in them, one would very definitely expect there to be about a 20% reduced activity of the gene product as compared to a 100 mitochondria control with no such mutational hits. The Examiner's scientific reasoning is very definitely faulty in that she tries to look at a single gene of a single mitochondria rather than a population of mitochondria, which is what is going to be measured in a blood sample!

Next, the Examiner argues, again without any scientific support or affidavit, that some lesions or mutations may occur in non-coding regions and thus would not affect protein production. This analysis, while perhaps applicable to a situation where one is looking at a single mitochondria, again misses the point for essentially the same reason. Where there is a *population* of mitochodria being tested (which there certainly would be if one were testing a blood sample or blood products as stated by the claim), there would necessarily be a vast range of mutations occurring in the mitochondria, some within coding regions and some outside of a particular coding region. Nevertheless, the distribution would be expected to be random and thus demonstrate a readily identifiable *correlation* between the amount of damage in any one gene, as measured by expression of that gene, and the amount of damage overall. The Examiner in fact confirms this by correctly stating that the "knockout of mitochondrial enzyme with a single mutation could cause dysfunction." That's precisely the point: in any population of mitochondria there will be a distribution of gene knockouts by mutation and the level of that distribution of knockouts, as reflected by the activity or amount of the particular mt protein or mRNA being measured will reflect the degree of DNA damage. If *every single* mitochondria in the sample has that particular mt protein or mRNA knocked out – whether that protein or mRNA is involved in ATP production or mitochondrial redox state – you darn well know that *that* patient has some real problems with their mitochondria!

Lastly, responding to the Examiner's allegation that the specification does not teach a direct tie between mt gene mutations and the activity of mt gene products, we would state that a direct tie between the amount of gene mutational damage and the expression of *any* given gene, mRNA, *etc.*, is, simply put, self evident, and the Examiner has presented no evidence to the contrary.

Quantity of Experimentation

Turning to the next section of the non-enablement rejection, that dealing with quantity of experimentation, the Examiner again fails to come forth with any cognizable evidence and merely states, incorrectly, in a conclusory fashion that there "are many other factors which would affect each of these quantities which may not be related to the amount of mtDNA damage." However, the Examiner notably fails to point to any such "many other factor" in either any scientific literature or in an affidavit as required by 37 CFR §1.104(d)(2).

Thus, as explained above, the Action fails to set forth a *prima facie* case of inoperability of the rejected claims.

D. Section 112, Second Paragraph Rejections

Next, the Action rejects claim 7 under 35 USC 112, second paragraph, due to an antecedent basis problem. To resolve this minor issue, Applicants have simply elected to cancel the claim as its intended subject matter is adequately covered by existing claims.

E. Section 102 Rejections

The Action next rejects claims 6 and 23 and anticipated by VenMurthy *et al.*

In response, it is submitted that no *prima facie* case of anticipation has been set forth, in that the Examiner has failed to explain how each an every element of the rejected claims is taught by VenMurthy *et al.* For example, present claim 6 reads:

> 6. A method of measuring the amount of oxidative stress in an individual, comprising the steps of:
>
> (a) collecting hematopoeitic tissue from said individual;

(b) measuring the amount of mitochondrial DNA damage in said tissue wherein such damage is indicative of oxidative stress in said individual.

Yet, the Examiner has failed to point out where, for example, VenMurthy teaches "measuring the amount of mitochondrial DNA damage." In contrast, VenMurthy simply looks at alterations in the banding pattern of mtDNA, which is in no way an attempt to "measure" the damage. This may well be the reason why VenMurthy failed to detect any differences between the controls, of which 9 of 9 exhibited abnormal bands, and the experimental, most all of which exhibited abnormal bands as well.

Accordingly, no *prima facie* anticipation by VenMurthy has been shown on this record.

E. Section 103 Rejections

Lastly, the Action enters various obviousness rejections of various of the claims over VenMurthy *et al.* and Yan *et al.*

We respectfully traverse and contend that the Examiner has failed to set forth a proper *prima facie* case of obviousness as there is clearly no motivation to combine these references. As noted by the Action, Yan *et al.* made an observation based on the mitochondria of diseased aortic atherosclerotic tissue as compared to normal aortic tissue. However, while VenMurthy makes reference to testing lymphocytes, *those* assays clearly failed to demonstrate *any* difference in the mtDNA mutations of positive versus negative control samples. Thus, since VenMurthy admittedly failed to demonstrate any difference it can in no way be said that the skilled artisan would seek to combine this reference with any reference, much less one like Yan *et al.* dealing with aortic tissue. Stated another way, there was clearly no expectation that were Yan to test the

lymphocytes of VenMurthy that such a test would be successful – indeed, the very VenMurthy reference itself suggests that such a test would not be successful!

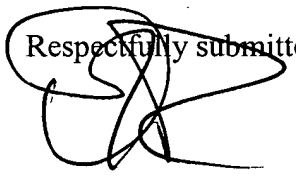
The Examiner is therefore earnestly requested to reconsider and withdraw the pending obviousness rejections, and pass the case to allowance.

CONCLUSION

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn so they may pass to issuance.

Should the Examiner desire to sustain any of the rejections discussed in relation to this Response, the courtesy of a telephonic conference between the Examiner, the Examiner's supervisor, and the undersigned attorney at 512-536-3055 is respectfully requested.

Respectfully submitted,



David L. Parker
Reg. No. 32,165
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 474-5201
(512) 536-4598 (facsimile)

Date: July 1, 2005